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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,741	12/20/2001	Shinichiro Kurosawa	OMRF:004US/SLH	9903

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/028,741	**Applicant(s)** KUROSAWA ET AL.	
	Examiner Claire M. Kaufman	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 May 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *13 June 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, ~~the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended~~.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-16*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

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Applicants argue that the cited passage (p. 2, lines 25-27 of previous Office action) from Esmon et al. (1999) refers to **rat** experiments by Gu et al. (2000) involved with inflammatory mediators of sepsis. The argument has been fully considered, but is not persuasive. Esmon et al. did original research in rats, but also discuss findings related to sEPCR in humans (references 74 and 75 cited on p. 255, col. 2). As stated in the previous Office action, "Additionally, it was reported (p. 255, col. 2, third full sentence) that soluble EPCR (sEPCR)was present at high levels in the plasma of normal individuals and was increased several fold in patients with diseases associated with hypercoagulation (autoimmune disorders and septic shock, specifically systemic lupus erythematosus (see #C8, Kurosawa et al., Fig. 1)."

Applicants argue that Esmon et al. and Gu et al. (2000) only speculate about use of monitoring plasma EPCR levels in humans and "Their data predicts that soluble EPCR levels may be linked to thrombin production in humans, but they do not test the prediction. They do not show data from patients or other humans in their study." The argument has been fully considered, but is not persuasive. Had Esmon et al. shown human data, the reference might have been relied upon for anticipation instead of obviousness. Nevertheless, Esmon is relied upon for teachings related to rats and to humans that, when taken in combination with the teachings of the other prior art relied upon, render the claimed invention obvious as discussed in the previous Office action.

Applicants cite *In re Vaeck* (Fed Cir. 1991) to support the need for likelihood of successfully practicing the claimed invention based only on animal studies. The argument has been fully considered, but is not persuasive. *Vaeck* deals with producing different proteins in cyanobacteria. It does not deal with the argument at hand, that is the predictability of a rat model sEPCR assay for human use.

Applicants argue that some prior art supports the use of animal models and some does not. The argument has been fully considered, but is not persuasive. This is correct and the applicability of an animal model to human patients is dependent on what is being modeled and analyzed. Applicability must be taken on a case by case basis. In the instant situation, the prior art supports use of the rat model for measurement of sEPCR for monitoring thrombin levels. It further should be noted that the claims are drawn to assaying not methods of treatment, which have additional considerations when evaluating the reliability of an animal model.

Applicants argue that the examiner dismissed Applicants' arguments as "simply "not persuasive"". This is incorrect as can be seen from the discussion of Applicants' arguments in the previous Office action (mailed 2/10/05) on pages 4-6. The discussion of murine and human mutations of the thrombin gene, while not directed to mutations affecting binding of thrombin to its receptor, does point to the correspondence of mice and human in thrombin gene function.

Applicants argue that Giudici et al. (1999) teach away from the instant invention, demonstrating that antithrombin therapy is minimally effective if at all. The argument has been fully considered, but is not persuasive. The instant claims are not drawn to therapy. They are drawn to monitoring thrombin levels in a patient undergoing anticoagulation therapy. Whether or not the therapy of Guidici et al. was successful, monitoring the success of the therapy was. Anticoagulation therapy is widely used for humans in need thereof.

Applicants argue that a critical aspect to understanding the difference between rodent and human in thrombin activity is that the PAR receptor(s) to which thrombin binds is different in mouse and human, leading to the conclusion that one cannot reasonably expect thrombin-related findings in rodents to be predictive of those in humans. The argument has been fully considered, but is not persuasive. It has been shown *e.g.*, Kahn et al., J. Clin. Invest., 1999) cited by Applicants on p. 7 of response, that humans use PAR-1 and PAR-4 receptors, while mice have no PAR-1 and use PAR-3 and PAR-4 instead. Even though there are different homologous receptors used in humans and mice, there is no expectation that the *intracellular* events are not at least on whole the same in rodents and humans. Further, the examiner has relied on teachings supporting this. Lower levels of rat sEPCR resulted from anticoagulant treatment and corresponded to reduced levels of thrombin (see Esmon et al., 1999). A corollary response was found in humans in that patients with a disease associated with hypercoagulation had higher levels of sEPCR (see previous Office action, p. 2, lines 19-24). Indeed, the prior art teachings do provide a reasonably expectation that as far as correlation of sEPCR levels with thrombin levels, rodents appear comparable to humans.

Applicants argue that the literature is replete with examples of murine results not being confirmed in humans and that mouse data cannot be used to support a method in humans, particularly in this instance. The argument has been fully considered, but is not persuasive. First, the results of Esmon et al. were from rats not mice, though it is contended that any

advantage or disadvantage would be expected to be true of most rodents, *i.e.*, rats and mice. Even though there are literature examples showing exceptions of rodent data not being predictive of human findings, there are a myriad showing the opposite. Each situation must be evaluated using its unique and pertinent information. It is maintained for the reason of record and as discussed here that the obviousness rejection which relies partly on teachings of methods used with rodents is valid. The prior art literature combines information from rodents with human data, and provides suggestions and motivation which would have provided the artisan of ordinary skill with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

June 16, 2005

LORRAINE SPECTOR
PRIMARY EXAMINER